Conference Report

Promoting Quality Laboratory Testing for Rare Diseases: Keys to Ensuring Quality Genetic Testing

May 20-21, 2004
Atlanta, GA

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I. Introduction

The **Promoting Quality Laboratory Testing for Rare Diseases: Keys to Ensuring Quality Genetic Testing** conference, organized by the Centers for Disease Control and Prevention (CDC), Emory University School of Medicine, the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH), the American Society for Human Genetics (ASHG), the American College of Medical Genetics (ACMG), the Health Resources and Services Administration (HRSA), and the Genetic Alliance, was held on May 20-21, 2004, at the Emory Conference Center in Atlanta, GA. Participants of the conference included more than 50 experts from government, academic institutions, professional organizations, laboratories, industry, healthcare payers, and patient advocacy groups. The main goals of the conference included: 1) to review the current rare disease testing landscape; 2) to discuss problems and concerns regarding the quality, availability, access, and resources for rare disease testing; 3) to identify needs and barriers to quality testing; 4) to explore potential approaches to promoting quality laboratory testing; and 5) to develop specific recommendations and action items for improving availability of and access to quality laboratory testing for rare diseases.

The meeting began with welcoming remarks by Dr. David Ledbetter, Director, Division of Medical Genetics, Department of Human Genetics, Emory University School of Medicine; Dr. Stephen Groft, Director of ORD, NIH; and Dr. Muin Khoury, Director of Office of Genomics and Disease Prevention (OGDP), CDC. Dr. D. Joe Boone, Associate Director for Science, Division of Laboratory Systems (DLS), Public Health Practice Program Office (PHPPO), CDC, gave an overview of the agenda and goals of the conference.

II. General Sessions

General Session I. Genetic Testing for Rare Diseases, Oversight Issues, and Public Needs

The first general session, moderated by Dr. Carol Greene, Office of the Secretary, Department of Health and Human Services (HHS), included the following presentations:

<u>Overview of Laboratory Testing for Rare Diseases</u>

Dr. Bin Chen and Andy Faucett, DLS, PHPPO, CDC, presented an overview of currently available rare disease tests and laboratories offering testing for rare diseases. A review of genetic tests listed in the GeneTests directory in 2000, conducted by OGDP and DLS, CDC, found that at least 95% of available genetic tests were performed for rare diseases and conditions. A more recent review of GeneTests indicated that, of the 1,039 diseases listed as of April 2004, clinical testing was available for 694 diseases, or 67%; whereas for the remaining 354 diseases, testing was for research purposes only. Among clinically available genetic tests, 78% are available from US laboratories and 22% are available only outside the US. Over the past 6 months, the net number of clinically available genetic tests has increased by 51, reflecting a combination of transition of "research only" tests to clinical testing, new tests offered by clinical laboratories, and

tests that are no longer clinically available. In addition, changes were noted in laboratory services, including a significant increase in laboratories offering clinical confirmation for mutations identified by research laboratories. The analysis also revealed that the average growth rate of genetic tests over the past 6 months was less than 10 new tests per month; in contrast, an average of 20 new rare diseases are described in the medical literature every month, while 60-100 new entries related to genetic research findings appear in the Online Mendelian Inheritance In Man (OMIM) database per month.

CLIA Oversight for Rare Disease Testing

Virginia Wanamaker, Deputy Director of Division of Laboratory Services, Centers for Medicare and Medicaid Services (CMS), provided an overview of the Clinical Laboratory Improvement Amendments (CLIA) regulations and the outcome-oriented survey process for laboratory performance. She specifically addressed CLIA compliance issues relating to genetic testing, and updated participants on the progress of the preparation of a Notice of Proposed Rule Making for establishing a genetic testing specialty under CLIA. In addition, she provided clarification on two "myths" regarding CLIA compliance – Myth 1 assumes that if a CLIA-certified laboratory sends a patient specimen to a research laboratory for testing and then confirms the test results of the research laboratory, the research laboratory does not need a CLIA certificate; and Myth 2 assumes that if a physician sends a patient specimen to a foreign laboratory, it is not subject to CLIA requirements regarding specimen referral and the foreign laboratory does not have to be CLIA-certified. Ms. Wanamaker emphasized that under CLIA, both the "research laboratory" in Myth 1 and the foreign laboratory in Myth 2 need to be CLIA-certified.

IRB Issues in Releasing Individual Test Results in Clinical Research

Glen Drew, Office for Human Research Protections (OHRP), provided an overview of the work of OHRP in assuring safety and protection of human subjects in HHS-supported research through responsibilities of the Institutional Review Boards (IRBs). Every institution engaged in human subject research conducted or supported by HHS must obtain an assurance of compliance approved by OHRP; OHRP also evaluates complaints and indications of noncompliance, and determines regulatory actions needed based on results of the institutional investigation. He highlighted the top 10 information elements that should be included in the informed consent document for clinical research, and concluded that whether test results could be disclosed, as well as the extent and conditions of disclosure, should be explained as part of the informed consent and adhered to during clinical research. Regarding genetic testing in research studies, OHRP currently does not have specific guidelines regarding CLIA compliance. It is left to individual IRBs to determine whether or not testing needs to be performed by a CLIA-certified laboratory if individual test results will be released to research participants and/or their care providers.

HIPAA Privacy Rule and Rare Disease Clinical Research*

Myra Moran, Office for Civil Rights (OCR), gave an overview of the HIPAA Privacy Rule and its implications for clinical laboratories, focusing on the requirements relating to the use and disclosure of protected health information by covered entities for research

purposes, records subject to CLIA, and the rights of the individuals with respect to that information. She specifically clarified the relationship between the Privacy Rule and CLIA regarding the right of patients or research participants to access their laboratory records. The Privacy Rule does not require clinical laboratories that are also covered health care providers to provide an individual with access to information if CLIA prohibits them from doing so. CLIA permits clinical laboratories to provide clinical laboratory test records and reports only to "authorized persons," as defined primarily by State law. The individual who is the subject of the information is not always included as an authorized person. Therefore, the Privacy Rule includes an exception to individuals' general right to access protected health information about themselves if providing such access would be in conflict with CLIA. In addition, for certain research laboratories that are exempt from the CLIA regulations, the Privacy Rule does not require such research laboratories, if they are also a covered health care provider, to provide individuals with access to protected health information, because doing so would result in the research laboratory losing its CLIA exemption. Nonetheless, in most cases, individuals who receive clinical laboratory tests will be able to receive their test results or reports through the health care provider who ordered the test for them.

A question was presented as to whether a covered health care provider may disclose health information about a third party, such as a family member's medical history, as necessary to treat a patient. For example, the provider may need to provide a genetic testing laboratory with the disease information of the patient's parents for purposes of diagnosing the patient. The Privacy Rule allows a covered entity, without the patient's authorization, to use or disclose protected health information, such as X-rays, laboratory and pathology reports, diagnoses, and other medical information for its own treatment purposes, as well as disclose the information for the treatment purposes to any health care provider. This includes sharing the information of a third party, such as a patient's family medical history, with another health care provider as necessary for the treatment of a patient. Additional information regarding the use and disclosure of protected health information to carryout treatment, payment or healthcare operations is contained in the HIPAA Rule. See 45 CFR § 164.506. **This summary is approved and cleared by the Office for Civil Rights (OCR) HHS.*

<u>Rare Genetic Diseases: Former SACGT Workgroup and the NIH-DOE Task Force on Genetic Testing</u>

Dr. Michael Watson, Executive Director of the American College of Medical Genetics (ACMG), reviewed the recommendations on rare disease genetic testing under the NIH-Department of Defense (DOE) Task Force on Genetic Testing and the work of the Rare Disease Workgroup established by the previous Secretary's Advisory Committee on Genetic Testing (SACGT). He also summarized results of a CLIA compliance survey conducted among ASHG members in 2002, which indicated that among the 99 respondents, 35 were non-CLIA laboratories releasing patient test results. The survey revealed that these laboratories either assumed they were not performing clinical testing since they did not bill for their services, or thought it too difficult to obtain a CLIA certificate. Dr. Watson pointed out that the respondents expressed interest in obtaining assistance with CLIA compliance. Among the types of assistance needed were guidance

for developing quality assurance programs, help to identify clinical laboratories willing to take on new tests, and educational workshops.

Clinicians' Perspective and Needs for Rare Disease Laboratory Testing

Dr. William Gahl, Clinical Director of the National Human Genome Research Institute (NHGRI) and Director of the Intramural Program of ORD, NIH, presented a pilot approach co-sponsored by NHGRI and ORD to bring molecular diagnostic tests for specific rare diseases to clinical use. This pilot program will fund several CLIA-certified laboratories, including Greenwood Genetics Center, GeneDx, and the Emory University Molecular Genetics Laboratory, to set up genetic tests for a number of disorders studied by NHGRI. The first group of tests to be developed includes rare diseases with less complicated mutations and is anticipated to cost approximately $5,000 per gene. These laboratories are expected to make the tests publicly available and provide testing on a fee-for-service basis for at least 10 years.

Newborn Screening Systems: A Model for Translating Science into Practice

Dr. Michele Puryear, Chief of Genetic Service Branch, Division of Services for Children with Special Health Needs, Maternal and Child Health Bureau (MCHB), Health Resources and Services Administration (HRSA), provided an overview of the vision and goals of the MCHB Strategic Plan to assure the highest quality of healthcare and to facilitate access to care. She summarized the present initiatives of the Genetic Service Branch and activities under Title XXVI of the Children's Health Care Act of 2000 to improve the ability of States to provide newborn and child screening for heritable disorders. Currently, HRSA is initiating projects to establish regional genetic service and newborn screening collaboratives for the 7 geographical regions in the country, which will strive to facilitate access to genetic expertise, services, and technology that providers and families need to diagnose and manage children identified with genetic disorders. Dr. Puryear also provided updates on the establishment of the Secretary's Advisory Committee on Heritable Disorders and the tasks of this Committee.

General Session II: Approaches to Providing Quality Testing for Rare Diseases and Conditions

The second general session included examples of current approaches to providing and assuring quality laboratory testing for rare diseases. This session was moderated by Dr. David Ledbetter. *(Note: Dr. Sego*lene Ayme, Director of Orphanet, France, was unable to attend the conference. A copy of her presentation at a February 2004 European Rare Disease Workshop was shared with participants to provide insights on European rare disease networks.)

Proposed Partnership between Research and CLIA-certified Laboratories

Dr. David Ledbetter, Emory University School of Medicine, reviewed a proposal made to the former SACGT, in November 2001, on the potential for partnerships between research laboratories and CLIA-certified molecular genetics laboratories to improve clinical availability of genetic tests for rare diseases. Dr. Ledbetter pointed out that providing research participants and/or their healthcare providers with test results

generated in non-CLIA-certified laboratories would present an above-minimal risk to research participants, due to the potential for errors in patient testing performed by non-credentialed laboratories lacking adequate quality assurance standards. He suggested that such a risk be considered a significant issue of human subjects' protection, which should be more carefully evaluated by OHRP at the national level and by IRBs at the local level. Dr. Ledbetter also described his efforts to establish a National Laboratory Network for Rare Disease Genetic Testing and proposed that this model be further discussed during the breakout discussion sessions of the conference.

The Johns Hopkins University Experience

Dr. Patricia Charache, Johns Hopkins University, shared her experience establishing a process to ensure quality of laboratory testing for patient care at the Johns Hopkins University. Specific strategies included a laboratory review program and a credentialing program for laboratory directors, under the principle that all laboratories providing testing used in patient care must meet the standards of CLIA and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). The outcomes for the laboratories testing for rare heritable diseases included transfer of clinical testing from small research laboratories to CLIA-certified pathology laboratories, discontinuation of patient testing in laboratories without CLIA certification, and employment of qualified laboratory directors. This process has resulted in substantial improvement in CLIA and JCAHO inspections. Dr. Charache concluded that education was critical to the success of this process; among other key programmatic considerations were avoiding bias, utilizing evidence-based data and the academic structure to effect changes, and providing information and support to all laboratories within the institution evenly.

Rare Orphan Genetic Disease Diagnosis – The University of Chicago Experience

Dr. Soma Das, Director of Molecular Genetics Laboratory, Department of Human Genetics, the University of Chicago, presented the experience of her laboratory in implementing, validating, and providing genetic tests for rare diseases since 1998. Her presentation highlighted specific issues on validation, quality control and result interpretation of testing for rare diseases. She indicated the increase in testing volume for rare orphan genetic diseases in her laboratory since its implementation. She discussed the costs of setting up testing for these disorders, and summarized factors important for laboratories to financially break even and to expand the number of tests available; which included implementation of a billing mechanism, increasing test volume, increasing testing personnel, and automation of testing technology. She also pointed out that the lack of funding and licensing conditions of gene patents could be factors negatively affecting laboratory growth.

The GeneDx Experience

Dr. Sherri Bale, President and Clinical Director of GeneDx, described the process of setting up a commercial laboratory dedicated to diagnostic testing for rare diseases, which included securing financial support and space, obtaining CLIA certification and Maryland State licensure, selecting initial tests to offer, and building the test menu over time. Since 2000, the number of tests offered by the laboratory has grown from 16 to over 80, and the volume has increased from 166 in 2000 to an anticipated 4000 patient

specimens for 2004. Dr. Bale suggested that the business model had worked successfully for her laboratory. She also shared problems encountered in offering rare disease testing, including obtaining proper informed consent, prenatal testing, lack of available proficiency testing program, significant increase in liability insurance costs, and licensing issues related to patented genes.

The Genetic Testing Quality Assurance Program in New York State

Dr. Michele Caggana, Section Head, Genetic Testing Quality Assurance Program, Wadsworth Center, New York State Department of Health, provided an overview of the New York State oversight for laboratories performing genetic testing for New York State residents. As Section Head, Dr. Caggana's responsibilities include approval of certificate of qualification for laboratory directors and assistant directors, review and evaluation of method validation submissions, review of survey results, analysis of questionnaire data, and review of non-permitted laboratory requests. She emphasized that for genetic testing; New York State requires laboratories to have specific approval for each test they perform. For any test submitted by a licensed medical practitioner for which no laboratory is approved, laboratories must submit a "Non-permitted Laboratory Request" together with information regarding the test to be performed, the referring laboratory, and the referral laboratory, the CLIA number of the referral laboratory, the patient, the referral, and justification for testing. Approval of such requests is based on continuity of care, the need for additional testing, and other considerations, but not for financial reasons. Dr. Caggana summarized that 1,326 non-permitted laboratory requests have been reviewed during the past 5 years, among which a significant portion were for rare disorders.

The Hospital of Sick Children Experience

Dr. Peter Ray, Director of the Molecular Diagnostic Laboratory of the Hospital for Sick Children, Toronto, Canada, described his laboratory's experience in providing genetic testing for rare diseases, with an emphasis on pediatric disorders. He shared issues of concern regarding result interpretation in mutation detection for Batten disease, mutation and carrier analysis for Duchenne muscular dystrophy, and sequencing-based testing methods. Dr. Ray pointed out that providing healthcare providers with adequate information on result interpretation was critical to assure appropriate understanding and use of test results in patient care. In light of this need, the Hospital for Sick Children has established a resource center for hospital physicians to provide information on testing availability, referral advice, and assistance with result interpretation and patient counseling.

General Session III: Translation of Gene Findings to Clinical Tests

The third general session, moderated by Dr. Steve Groft, included a series of presentations on developing rare disease laboratory tests based on research findings and integrating new tests into practice.

Office of Rare Diseases Experience in Rare Disease Gene Testing

Dr. Giovanna Spinella, Director of Extramural Research program, ORD, NIH, began her presentation with an overview of ORD's responsibilities under the Rare Disease Act of 2002, which include stimulating and coordinating research on rare diseases; developing information resources to meet the needs of the public, health professionals, patients and families; and preparing reports to Congress on rare disease research, education, and advances. She highlighted perspectives of the patient community and the research investigators in the process of finding disease genes and translating the findings into clinical testing – patients participating in research often desire to know their mutation status because they view gene discoveries as a critical first step towards understanding their disease and developing specific treatment; on the other hand, the small number of research investigators for each specific rare disease, who may become experts in test development, often feel responsible to provide testing information back to patients and families. However, the perceived difficulty in attaining CLIA compliance and barriers to transferring testing to clinical laboratories, due to the lack of CLIA-certified laboratories willing to take on low volume testing for rare diseases or burdens in establishing licensing agreements, could result in research laboratories releasing patient test information without a CLIA certificate. Dr. Spinella summarized additional issues raised by researchers to ORD, including whether a non-CLIA-certified research laboratory could provide information back to research participants, the role of IRBs in gate-keeping this issue, the lack of genetic tests for many rare diseases, and inconsistent access to testing even when it is available. She concluded the presentation by emphasizing the need to improve availability of rare disease gene testing and the importance of translating research findings into validated clinical testing.

The Office of Orphan Products Development Grant Program

Dr. Janet Whitley, Office of Orphan Products Development (OOPD), the Food and Drug Administration (FDA), gave an overview of the Orphan Products Grant Program, which supports clinical research demonstrating promise for the diagnosis and treatment of rare diseases. Under this grant program, 36 biological products for rare diseases have been brought to market together with hundreds of scientific publications, abstracts, and presentations. Dr. Whitley also described OOPD's responsibilities in the evaluation of humanitarian use devices (HUDs), which are defined as medical devices intended to benefit patients in the diagnosis and/or treatment of a disease or condition that affects or is manifested in fewer than 4,000 individuals per year in the US. HUD applications are first reviewed by OOPD to determine the appropriateness of the rationale and the intended population; then the device must be evaluated for safety and probable benefit by another FDA program under the Center for Devices and Radiological Health (CDRH).

Humanitarian Device Exemptions (HDE) and Investigational Device Exemptions (IDE) Programs

Dr. Elizabeth Mansfield, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD), CDRH, FDA, reviewed the responsibilities of her program for reviewing and approving device applications under the HDE and IDE regulatory provisions. She discussed a number of commonly expressed concerns regarding HDE approvals, including whether the 4,000 US patients per year is the right limit for both therapeutic drugs and diagnostic devices, whether the post-market requirements for IRB approval and

non-profitability are appropriate, and why so few HDE applications have been submitted to FDA. Dr. Mansfield suggested that, because of the restrictions to HDE, test developers might not consider it an attractive option; they might instead choose to offer testing for rare diseases as laboratory-developed, or "home brew", tests to be able to make a profit.

Development of a Genetic test for Pseudoxanthoma Elasticum (PXE): Patients' Role in Research Translation

Sharon Terry, President and CEO of the Genetic Alliance and Executive Director of PXE International, Inc., shared the process of developing a mutation detection assay for PXE, an inherited disorder affecting connective tissue in multiple organs, with the support and participation of PXE International, Inc., an international patient support organization. She highlighted a number of challenges and problems in rare disease research, including limited pools of participants, small collections of patient samples, competitive and fragmented research environment, poor confidentiality protection for patients, variable informed consent process, inaccurate disease characterization, limited reporting of test results to participants, and inadequate funding. To assist in research translation, the Genetic Alliance initiated a BioBank project in 2003 to establish a repository of biological samples associated with clinical data, to facilitate accelerated, coordinated, and ethical genetic research.

Genetic Testing for Rare Diseases: A Payer Perspective

Dr. Morris Mellion, Associate Medical Director, Blue Cross and Blue Shield Association (BCBSA), presented issues considered by BCBSA in determining whether a rare disease test could be covered and reimbursed. In general, to be covered by the health plan, the test or technology must meet appropriate FDA and CLIA regulatory requirements and must be scientifically validated. He outlined 5 criteria that the BCBSA Technology Evaluation Center uses in conducting technology assessments, including 1) the technology must have final approval from the appropriate governmental regulatory bodies, 2) the scientific evidence must permit conclusions concerning the effect of the technology on health outcomes, 3) the technology must improve the net health outcome, 4) the technology must be as beneficial as any established alternatives, and 5) improvement must be attainable outside of investigational settings. Subsequently, Dr. Margaret Piper, Technology Evaluation Center, BCBSA, explained how these criteria are used in evaluating and determining the clinical implementation of a number of genetic tests, including molecular genetic testing for the HFE gene related to hereditary hemochromatosis, BRCA 1/2 genes for inherited susceptibility to breast cancer, APC and mismatch repair genes for hereditary colon cancers, and ApoE testing for Alzheimer disease. She acknowledged the difficulty in gathering data for rare disease testing due to the low prevalence of rare diseases, but also pointed out the opportunities for assessment studies in this area. For example, the small sample size might be more representative of the affected population. Dr. Piper concluded with a summary of the payer's perspective for rare disease testing, emphasizing the following needs: 1) to agree on a workable definition for rare disease, 2) to apply regulatory standards to ensure quality, 3) to improve data collection to aid in evidence-based decision making, 4) to improve technology assessment, and 5) to handle exceptions on a case-by-case basis.

III. Breakout Discussion and Recommendations

Following the general sessions, participants formed three breakout groups in concurrent discussion sessions during the remainder of May 20 and early morning of May 21. Because of the broad scope of the discussion, each breakout group was charged to address a subset of the issues and also ensure that overlapping issues were adequately considered by participants with expertise needed.

Breakout Group A - Promoting Quality Testing. This group was charged to develop recommendations for actions needed and identify issues to be further discussed for promoting and assuring the quality of rare disease tests in clinical settings and laboratories providing patient testing for rare diseases and conditions. Topics addressed by this group included:

- Strengths and weaknesses of current strategies and approaches to assessing and evaluating the quality of laboratory testing for rare diseases;
- Applicability of available guidelines for assessing and evaluating quality of rare disease testing, recognizing that formal or standard proficiency testing (PT) or external quality assessment (EQA) programs are not available for the majority of the rare disease tests;
- Issues related to international test referrals or cross-border testing, recognizing that currently for many rare conditions, a patient specimen has to be sent to another country to be tested;
- Data needs for assessing the quality of current testing, identifying areas needing improvement, and developing recommendations and strategies for best practices;
- Responsibilities of laboratories in listing, announcing, or advertising their testing services; and
- Appropriate roles of government, laboratories, professional organizations, industry, academic institutions, healthcare providers, patients, and others in promoting quality rare disease testing.

Breakout Group B - Transferring Tests from Research Phase to Clinical Use. Group B was charged to develop recommendations for translating genetic findings into clinical testing, taking into consideration stages from clinical research, disease gene identification, test development, through validation and implementation in patient care. Discussion of this group focused on the following issues:

- Strengths and limitations of current mechanisms for moving potential tests from the research phase to clinical use;
- Networking approaches needed to facilitate and encourage translation;
- Validation of newly developed rare disease tests during each step of the translation process, from patient classification, gene identification, test or test system development, through implementation in clinical laboratory setting or as part of a public health program;
- Data collection and compilation needed to facilitate research translation, test validation, and review or evaluation of new tests;

- Impact of technology on research translation and test availability;
- Oversight and gatekeepers needed to ensure quality of each step of the translation process; and
- Roles of government, investigators, professional organizations, industry, academic institutions, healthcare providers, patients, research participants, and others in the translation process.

Breakout Group C - Access, Data, and Educational Needs. This group was charged to develop recommendations on systems and mechanisms needed to improve the availability of, access to, and information dissemination for rare disease testing. Issues considered by this group included:

- Needs and challenges in ensuring continued availability of quality rare disease testing, recognizing that individual rare disease tests are often available from a single or only a few laboratories and from laboratories primarily conducting research;
- Mechanisms that can be explored to assist in implementation and provision of testing;
- Improving coverage and reimbursement for rare disease genetic tests;
- Mechanisms needed for data collection, assessment, and synthesis to aid in evidence-based decision making by oversight agencies, insurers, and other data users;
- Educational needs and roles of all stakeholders in improving public knowledge of quality testing; and
- Practical mechanisms for information dissemination and education.

Subsequent to the breakout discussion, participants returned to a general session to hear the reports from each breakout group and to provide additional input. All three group reports were received with enthusiasm. Recommendations were made by each group regarding the areas of needs to be addressed, actions needed; issues to be further discussed, and key organizations for the suggested activities. A number of overarching premises and consensus were recognized in addition to recommendations for specific aspects of rare disease testing.

III-A. Premises

1. Clinically available genetic tests and research translation efforts needed to develop clinical testing services are woefully behind the pace of basic discoveries in genetics and genomics.
2. High quality testing is the goal of all phases of the translation process, from the research phase to clinical laboratories.

III-B. General Recommendations

1. Affirmation of CLIA standards for tests used for clinical purposes. When test results are to be shared with patients, research participants, or their healthcare providers, whether during clinical research, transition of potential tests from research to clinical use, or the clinical testing phase, the entire testing process,

including specimen collection and processing, analytical procedures, and result reporting, should be performed by CLIA-certified laboratories.

2. Education is needed regarding CLIA and other requirements for releasing individual-specific results in clinical research. Research investigators, laboratory directors, clinicians, pathologists, patients and families, research participants, and other users of laboratory services should be considered the target audience. It is important to have strategies in place and consensus on the teaching materials before initiating the educational activities, to minimize adverse effect on access to testing. With assistance from CMS and CDC, professional organizations and funding agencies should take a leading role in the development of educational programs and teaching aids and in information disseminating.
3. Provide education for IRBs regarding CLIA and the role that IRBs should have in safeguarding the release of individual test results in clinical research. OHRP should lead this activity, with assistance from CMS, CDC, funding agencies, and professional organizations to develop educational strategies, materials, and process.
4. Develop mechanisms and guidelines for determining the clinical readiness of a potential test. Issues to be further explored include how newly developed rare disease tests should be validated, and how analytic validity, clinical validity, and clinical utility should be established for rare disease tests with an often limited patient population.
5. Establish mechanisms and strategies to promote quality data collection during each step of test development through clinical application, in order to 1) facilitate translation of potential tests to the clinical setting, 2) improve result interpretation and use in patient management, 3) assess impact and benefits of testing on health outcomes, and 4) improve access to quality testing.

III-C. Recommendations for Promoting Quality Rare Disease Testing

Recommendations in this area were developed by Breakout Group A and reported by Drs. Patricia Charache and Carol Greene. After considering strengths and weaknesses of current strategies to assuring quality testing, applicability of available guidelines for quality assessment, data needs, and actions needed for promoting quality rare disease testing, the group made the following recommendations:

<u>Strengths and Weaknesses of Current and Proposed Approaches</u>

1. The Johns Hopkins University approach. The group discussed the approach presented by Dr. Patricia Charache and considered a model in which all research laboratories providing specific information back to patients or research subjects become CLIA-certified. It was agreed that this model would ensure basic quality laboratory practices and compliance with applicable regulatory requirements; however, its broader transferability is unknown since it requires strong institutional commitment and close collaboration with a department. In addition, there are both real and perceived barriers, such as the risk of discontinuing testing services, the lack of resources needed for implementation, as well as laboratory personnel and leadership issues.

2. New York State Program. The group agreed that the New York State program provides peer review of method validation, assures quality performance of laboratory testing, and enables quality assessment in association with laboratory surveys.
3. Partnerships for CLIA laboratories to provide confirmatory testing for mutations found in non-CLIA laboratories. A general concern was expressed for the likelihood of false negative results associated with this approach, since only positive findings are sent for confirmation. The group discussed various specific approaches under this model, and felt that some are evidently not in compliance with CLIA while others need further review and input from the oversight programs to determine their appropriateness. In addition, this model does not solve the problem of research laboratories desiring or being expected by research participants to share both negative and positive test results.
4. The proposed European approach based on benchmarking. It was agreed that if appropriate benchmarks for each phase of the testing process can be determined, they will be useful to set internationally acceptable standards for rare disease testing and cross-border test referrals. However, concerns were expressed about difficulties in developing appropriate benchmarks for rare disease testing.
5. Test referral to non-US laboratories. It was agreed that sending specific rare disease tests to non-US laboratories is currently necessary but also problematic; therefore, standards are needed both for specimen shipping and tracking documentation and for the validity and quality of the testing. In addition, CLIA requirements, US and international privacy regulations, and other requirements may impose restrictions both on cross-border test referrals and on obtaining information necessary for test selection, result interpretation and reporting. The group also noted that certain "borderless" laboratories may be able to facilitate sending specimens and test results across borders and may provide a model for addressing transborder testing; however, the use of these laboratories can be problematic when contact information for the testing laboratory is not provided and test results are transcribed or edited on the report issued to the referring institution.
6. The pediatric oncology group model. The group recognized the success of this model in setting guidelines that maintain the quality of clinical services and research investigations. It was agreed that further information on this model is needed to understand how it might apply to and be helpful for the rare disease testing community.

<u>Areas of Needs</u>

1. Guidance and quality indicators need to be developed for all testing phases, i.e., the pre-analytical, analytical, and post-analytical phases of rare disease testing. These guidelines need to be achievable and reasonable.
2. When test results are to be shared with patient(s) or provider(s), the pre-analytical, analytical, and post-analytical phases of testing should be performed by a CLIA-certified laboratory or an equivalent laboratory if the test is referred to a non-US laboratory.

3. Multiple approaches may be required to address the needs for quality testing while maintaining access to testing services, in recognition that –
   - CLIA requirements are minimum standards and not comprehensive for rare disease genetic testing;
   - Requiring CLIA certification precludes referring tests to many foreign laboratories offering rare disease tests not available within US;
   - CLIA requirements and other guidelines inadequately address key pre-analytical and (especially) post-analytical factors pertaining to test interpretation and result reporting; and
   - CLIA certification is inadequately enforced, known to, or understood by research laboratories performing patient care testing.
4. Mechanisms need to be developed to ensure accuracy of both positive and negative test results, in light of the growing services to confirm mutations identified by non CLIA-certified laboratories. Models to consider may include 1) research laboratories attaining CLIA certification, 2) partnering between research and CLIA laboratories, and 3) partnering between clinical laboratories.
5. In developing quality assurance strategies, non-DNA-based rare disease genetic testing should be considered in addition to molecular tests.
6. In considering efforts to improve the availability of rare disease testing, the inherent challenges of translational research and development of clinical services need to be recognized to avoid setting unrealistic expectations and to promote development of appropriate strategies and approaches.
7. Recommendations and action items suggested need to be followed through.

<u>Recommended Next Steps</u>

After identifying critical issues in rare disease genetic testing, the group developed recommendations for actions needed to assure quality testing, with considerations for organizations that should play key roles in the recommended activities.

1. Define quality standards for rare disease genetic testing through the following actions:
   a. Establish specific requirements for genetic testing under CLIA. HHS should accelerate its current pace in developing the proposed CLIA regulation for genetic testing.
   b. Establish quality indicators appropriate for rare disease testing, recognizing the limited availability of disease information, laboratories performing testing, quality control materials, and external quality assessment programs. The group agreed that this is an especially challenging area, and suggested that ACMG take the lead in collaboration with CDC.
   c. Establish validation guidelines for rare disease genetic tests and criteria for evaluating their analytical and clinical validity. The group agreed that this is also an especially difficult issue, and can be addressed in concert with (b) above.
   d. Establish standardized *generic* (i.e., not disease-specific) protocols for results reporting and for pre-analytic issues. ACMG could take a lead here in partnership with other standard-setting organizations, such as the

College of American Pathologists, the Association for Molecular Pathologists (AMP), New York State, NCCLS, and with help from the Clinical Laboratory Improvement Advisory Committee (CLIAC).

e. Enhance data collection and analysis, probably by a central facility to allow data sharing and genotype-phenotype correlation. Initiatives from major mutation databases, such as those affiliated with the Human Genome Variation Society (HGVS), should be supported. CDC and NIH should work closely to expand current efforts and develop evaluation and monitoring systems.

2. Further explore cross-border testing issues with international partners, especially with respect to international and US privacy regulations, CLIA certification, and overarching issues regarding assuring quality of global rare disease testing. The group suggested that CDC convene international colleagues to address these issues and develop strategies for moving forward.
3. Evaluate adequacy of current strategies to monitor testing and laboratory quality, and collect data on current practices and outcomes to 1) help identify problems, 2) suggest possible solutions, and 3) forecast and track impact of solutions on quality and access. The group felt that such assessment studies are critical for quality improvement but was unable to identify a specific group to lead in this area.
4. Provide education for IRBs, researchers, laboratories, and users of laboratory services regarding CLIA and other requirements to promote quality testing, as stated in Overarching Recommendations 2 and 3.

<u>Issues to Be Further Discussed</u>

1. What role professional organizations, government, and other players can play in setting quality standards or accreditation programs for rare disease testing? The group felt various models should be considered, including the European benchmark model, the Johns Hopkins University strategies, and the New York State approach.
2. How practical mechanisms should be established to balance quality and access/availability of testing – to ensure quality without imposing undue burden or restrictions on testing access, and to enhance availability and access without compromising quality? The group felt this is a critical issue that needs to be further discussed in conjunction with the recommendation on CLIA compliance for all patient testing, to determine which strategies will be useful and which will be counterproductive.
3. How should criteria be established for determining whether a rare disease test is appropriate for use in clinical settings? The group considered several options, including adoption of arbitrary criteria for test acceptability if the test identifies a defined percentage of known mutations for the disease or detects mutations in a specific patient population. However, the group also recognized the obligation to provide patients with access to testing that can generate helpful information for their families, even if limited information is available regarding penetrance and sensitivity due to the rarity of the disease.
4. To what extent should quality assurance strategies focus on the laboratory and to what extent should they focus on the test? The group felt a two-pronged approach

would be needed and recognized the need to have further discussion on how the two aspects could complement each other in assuring quality testing.

5. How should strategies be developed to assure appropriate result interpretation and patient counseling without excluding qualified professionals or specialists? The group discussed the New York State approach and the Johns Hopkins University model, in which the institution determines whether non-pathology laboratories may provide patient testing based on their qualifications. It was felt that if guidance were to be set forth by professional organizations or the government, appropriate expertise should be recognized to avoid disruption of quality service.
6. It was agreed that data are needed in the following areas in order to make more specific recommendations:
    a. Practice assessment on current rare disease testing;
    b. Information and better understanding of practices and problems in the pre- and post-analytic phases, including informed consent, information provided in test reports, and other considerations;
    c. Information on personnel in laboratories performing rare disease testing;
    d. Information on both tests and laboratories offering rare genetic disease testing that are not listed on GeneTests:
    e. Information on research laboratories releasing patient-specific test information and their concerns, to help i) develop practical educational means for CLIA compliance, ii) understand the impact on access associated with enforcing CLIA, and iii) minimize adverse impact without compromising quality;
    f. Practices within academic institutions in tracking laboratories doing rare disease testing and encouraging them to have quality assurance measures in place, to assist in exploration of funding needs and mechanisms.
7. A pilot generic or methodology-based proficiency testing project should be considered for rare disease tests not included in available PT/EQA programs.
8. Explore models of “equivalency” determination by CLIA for foreign laboratories.
9. Convene working group of international partners to consider cross-border issues relating to international test referral and sharing of information for clinical and research purposes, including consideration for privacy (HIPAA and other national and international privacy rules), CLIA, and international trade issues.
10. To promote quality patient testing in clinical research, develop a requirement for NIH grant applications, e.g., a checkbox, to ensure test performance in CLIA-certified laboratories if results are to be released to research participants or their healthcare providers.
11. Activities are needed to make the currently available educational resources more visible.
12. Consider implications of all strategies and policies proposed for non-DNA based tests.
13. Should there be a mechanism for monitoring the announcements and advertisements laboratories make regarding their testing services? The group was concerned about the inability to know the quality, reliability, or validity of the tests advertised, and felt further discussion is needed on responsibilities of laboratories for truth in advertising.

III-D. Recommendations for Transferring Tests from Research Phase to Clinical Use

Recommendations in this aspect was developed by Breakout Group B, which was charge to consider issues related to translational research and moving potential tests from research phase to clinical setting. Discussion of this was moderated by Drs. Joann Boughman, Steve Groft, and Giovanna Spinella. Dr. Boughman summarized the following recommendations and issues identified by the group:

Recommendations

1. Affirmation of CLIA standards when tests are used for clinical purposes, as stated in Overarching Recommendation 1. In conducting clinical research or during transition of potential tests from the research phase to clinical use, when individual-specific test results are shared with patients, research participants, or their healthcare professionals, the entire testing process, including specimen collection and processing, analytical steps, and result reporting, should be performed by CLIA-certified laboratories. Approaches to consider may include research laboratories becoming CLIA-certified or partnership between research and clinical laboratories so that clinical testing is performed by the clinical/CLIA-certified laboratory.
2. Enhance infrastructure to gain momentum to facilitate the rare disease translational process. The following needs were identified for the research and clinical areas respectively:
   1) For the research community:
      - More obvious support mechanisms for translational research;
      - Education of researchers regarding CLIA requirements for laboratories providing patient testing and other requirements pertaining to releasing individual-specific results in clinical research;
      - Mechanisms for developing partnerships between research and clinical laboratories, including, for example, providing possible contacts and a list of laboratories that could function as a resource;
      - Education and training for IRBs and institutions to improve understanding of CLIA requirements and the role of IRBs in safeguarding the translational process;
      - NIH ORD, ASHG, and ACMG should consider organizing and/or sponsoring activities to address some of these needs; OHRP should take the lead for IRB education.

   2) For the clinical community:
      - Resources and funding mechanisms in response to requests from research laboratories. The NIH model that Dr. Gahl presented could be considered as a practical approach in support of the needs of the NIH clinical research programs as well as individual laboratories.
      - Network/database of resource laboratories, to facilitate the following activities:

- "Match making" capabilities among clinical laboratories, research laboratories, and advocacy groups regarding test needs and stage of development;
- Access to mutation databases to allow genotype –phenotype correlation;
- Appropriate quality assurance mechanisms within the network for confirmation or backup services and quality control/quality improvement purposes;
- Data sharing between and among research and clinical laboratories to improve interpretation and utility of test results.

- NIH ORD, HRSA, and AHRQ consider organizing and/or sponsoring activities to address these needs.

3. Set forth professional guidance for transferring potential tests from research to clinical use. Guidance might be needed from different professional organizations, including ASHG, ACMG, AMP and organizations representing pathologists, to address the needs and issues specific for their members.

<u>Recommended Next Steps</u>

1. Establishment of Rare Disease Testing Networks to include both DNA-based and biochemical testing for genetic diseases. It was suggested that a steering committee be formed to include representatives from government agencies, professional organizations, and patient advocacy groups; and that stakeholders include laboratorians, clinicians, researchers, advocacy groups, payers, and other users. A $5,000 contribution was proposed for founding members to initiate the network activities. Initial activities of the network should include:
   1) Communication and coordination – members of the network and the steering committee will need to get together to discuss steps needed to move tests that are only available on a research basis to clinical testing.
   2) Engage researchers – establish a web-based resource to provide information on how to contact and make request to the network and to serve as an educational mechanism.
   3) Develop process and guidelines for validating rare disease tests and for establishing the analytical validity, clinical validity, and clinical utility of rare disease testing.
   4) Data pooling – use information from mutation databases and clinical correlation studies to compile data needed to facilitate research translation and test validation. The need for general or specific data format will be considered to aid in determination of genotype-phenotype correlation with a small number of positive cases.
   5) Seek additional support for continuation, enhancement, and formalization of the network, through grant applications, response to RFAs, and other mechanisms.
2. Development and dissemination of meeting materials to involve additional stakeholders and engage the broader community.

3. Planning for a follow-up conference to convert recommendations developed into projects and action items; and develop recommendation for issues that need to be further addressed.
4. Development of professional guidelines for transferring potential tests from research phase to clinical setting.

Issues to be Further Addressed

1. Incentives for data sharing. It was recognized that incentives need to be established to encourage data sharing between and among research and clinical laboratories. Incentives could include authorship on publications but the scope and options need to be more broadly considered.
2. Determination of if or when a test is ready for clinical use. It was recognized that the transition point is when individual-specific test information is released, and that currently the decision is left to laboratories to make. Therefore, issues that need to be further explored include how newly developed rare disease tests should be validated, and how analytic utility, clinical validity, and clinical utility should be established for rare disease tests when the number of positive cases and families is often limited or very small.
3. Non DNA-based rare disease testing. It was recognized that availability of quality, accessible non DNA-based rare disease testing, such as biochemical genetic testing, also need to be improved; but there are specific challenges in transferring biochemical tests from research to clinical use. These challenges may be further discussed at the next conference.

III-E. Recommendations on Access, Data, and Educational Needs

Recommendations in these areas were developed by Breakout Group C, after discussing issues regarding the needs and challenges in ensuring continued availability of quality rare disease testing, improving coverage and reimbursement, data collection, and practical mechanisms for information dissemination and education. Dr. Roberta Pagon and Andy Faucett moderated and reported the discussion of this group. Among the recommendations and needs identified are the following:

Overarching Needs

1. Education is needed for researchers regarding their role in ensuring quality of the continuum from bench to bedside, for providers on test availability and appropriate use, for IRB groups on their role in safeguarding the research and clinical interface, for patient groups on setting appropriate expectations for potential or available testing, and for all groups on the availability, quality and efficacy of testing.
2. Partnerships need to be modeled and eventually required and encouraged by funding agencies to build relationships between investigators, clinical labs, patient groups, clinicians and payers that allow two-way learning. Professional organizations could create a pool of willing groups to participate in pilot projects. As a short term goal, funding agencies should require patient testing that is part of

a clinical research study to be performed in CLIA-certified laboratories, with assistance of IRB review.

Recommendations on Improving Access to Rare Disease Testing

The group spent considerable time discussing access and decided to focus on pre-market, market and post-market factors that affect access:

1. Pre-market phase. The group discussed issues affecting public awareness of potential tests, which could deter understanding of a potential test's clinical utility and integration to clinical care. The following recommendations were developed to address the needs in the pre-market phase:
    a. The cost of test development needs to be subsidized and business models showing how this can be accomplished need to be publicized.
    b. Models on how to show clinical validity and utility with limited populations need to be developed.
    c. Models of linking research laboratories with clinical laboratories in same or other institutions can be considered, to help promote a shift from all-service laboratories to niche laboratories specializing in particular rare disease tests.
    d. Funding agencies should consider including data collection on clinical validity and utility as an important goal in supporting research associated with development of new tests.
    e. Biobanks and repositories of patient samples need to be encouraged to facilitate test development, test validation and data collection.
2. Market phase. The gatekeeper-consultant systems need to be strengthened to direct healthcare providers to the right test performed by a qualified and experienced laboratory.
    a. Strategies need to be developed to help determine whether the appropriate test is available and make the information available to healthcare providers.
    b. The advantages and disadvantages of free-standing laboratories and university-based or academic laboratories need to be explored. When a test is only available from an academic laboratory, it is often not covered by insurers because the laboratory is "out of the network". Efforts need to be considered to improve coverage and reimbursement for such "niche" tests, and to explore strategies for laboratories offering these tests to become "in-network" providers.
    c. Education outreach should be considered for provider representatives and case managers from the insurance industry on rare disease test availability and use.
3. Post Market phase. The group identified the following needs:
    a. Involve primary care and other healthcare providers in the process to obtain data for evidence-based outcomes associated with quality testing; and
    b. Create an expectation that healthcare providers should provide adequate clinical information with test request to enable appropriate interpretation and utilization of test results in patient management.

Recommendation on Mechanisms and Infrastructures Needed

The group considered mechanisms needed for determining when a test is ready for clinical use, for making test information available to healthcare providers, for assessing

the impact of the test result on patient care, and for addressing the cost and reimbursement issues. The following next steps were recommended as a result of the discussion:

1. Develop a transition model for moving potential tests from research phase to clinical use.
    a. Federal research funding agencies need to develop the expectation and the process for such transition to include efforts of research laboratories, clinical laboratories, and patient support groups to enhance data collection.
    b. Expert groups should be developed to set guidance for test readiness and data collection for rare diseases. Past examples that can be considered include newborn screening programs, experience of the Ataxia Molecular Diagnostic Testing Group, prenatal maternal serum screening programs, and the Tay-Sachs screening program.
    c. Develop strategies to bring together the needs and interests in a potential test with the expertise and resources for test development, to facilitate the determination of its clinical readiness and to move the transition process forward. The group recognized the significant role that patient advocacy groups can have during this process.
2. Develop mechanisms for providing test information to healthcare providers. It was agreed that MD Consult or similar resources used by clinicians should be considered as possible mechanisms. In addition, the group recommended that professional organizations, particularly the American College of Physicians, the American Academy of Pediatricians, the Society of General Internal Medicine, and other professional groups representing healthcare users of laboratory services should be encouraged to develop guidelines regarding genetic testing for their memberships.
3. Develop mechanisms for determining how test results influence patient care and health outcome. It was agreed that data collection on clinical impact needs to be incorporated in the process of bringing a test to market. The group suggested exploring a "zero sum" model to bring all interested parties and stakeholders together to jointly develop approaches that are practical and beneficial for all parties. Focused discussion on this issue is recommended for the next meeting.
4. Strategies to address the cost issues. It was recognized that costs of clinical tests are highly influenced by liability concerns and that federal legislation similar to that for childhood and adolescent immunization might be needed to provide cost relief. The group recommended exploring a proposal that might reduce liability, by forming a network of laboratories to enable inter-laboratory comparison, service back-up, and other quality assurance measures.
5. Strategies to improve reimbursement schedule. It was pointed out that coverage and reimbursement for a new test can be influenced by public pressure, standards of care, and available data on clinical validity and utility. The group agreed that redefining billing codes to replace the current one-size-fits-all system is a long term goal; however, the need was recognized to reflect the value of rare disease genetic testing and associated clinical services through billing codes. The group recommended developing ways to educate payers about rare disease testing and

why costs may be higher, and then refining standards of care as payers start providing coverage and their understanding of the tests evolves.

IV. Immediate Outcomes of the Conference

At the conclusion of the conference, the following immediate outcomes and next steps were formed:

1. Six reference laboratories (the Emory University Molecular Genetics Laboratory, the Baylor Medical College Molecular Genetics Laboratory, the University of Chicago Molecular Genetics Laboratory, GeneDx, the UCLA Rare Disease Testing Laboratory, and the Hospital of Sick Children Molecular Diagnostic Laboratory) expressed interest in the proposed network approach and became initial members of a North American Rare Disease Laboratory Network.
2. ASHG will organize educational workshops for members to promote understanding of CLIA requirements and other quality issues in the rare disease research-clinical interphase, and is poised to develop a policy statement to address issues related to releasing individual-specific genetic test results in clinical research studies.
3. OHRP is committed to providing education to IRBs regarding CLIA certification and their role in safeguarding the release of individual test results in clinical research. Initial activities will include discussion among IRBs through the OHRP listserv, invited presentations on CLIA, and focused workshop at the IRB annual meetings.
4. A follow-up conference is needed to convert recommendations developed into projects and action items, and develop further recommendations for issues that need to be further addressed.

Participants expressed appreciation for conference organizers, particularly CDC, NIH ORD, and Emory University, for organizing and supporting the conference. It was suggested that the presentations, breakout group reports, and the conference summary be posted on the CDC website to make the information and recommendations available to the public and to help obtain additional input for moving the process forward. The follow-up conference, proposed to be the “Integration Conference”, will be held in 6 months in Washington, DC.